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EXAMINER	
LIU, SUE XU	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/056,348	BURCH ET AL.	
	Examiner	Art Unit	
	SUE LIU	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38 and 47-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38, and 47-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/19/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Claim Status

2. Claims 1-37 and 39-46 have been cancelled.

Claims 66 and 67 have been added as filed on 4/13/09.

Claims 38, and 47-67 are currently pending.

Claims 38, and 47-67 are being examined in this application.

Priority

3. This application is a continuation of 09/154,354 (filed 9/17/1998; now US Patent 6,552,031), which claims benefit of 60/059,195 (filed 9/17/1997).

Information Disclosure Statement

4. The IDS filed on 11/19/07 has been considered. See the attached PTO 1449 form.

Claim Objection(s) / Rejection(s) Withdrawn

5. In light of applicants' amendments to the claims and supporting arguments, the objection against Claims 57 and 58 in the previous office action is withdrawn.

6. In light of applicants' amendments to the claims, the following claim rejection(s) as set forth in the previous office action is(are) withdrawn:

Claim 56 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejections Maintained

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Baker, Friedel and Eversmeyer

9. Claims **38**, **47**, **48**, **50-52, 62, 63** and **66** as amended or originally filed are rejected under 35 U.S.C. 103(a) as being unpatentable over **Baker** et al., (US Patent 4,569,937; 2/11/1986; cited previously), in view of **Friedel** et al (Drugs. 1993. Vol. 45 (1): 131-156; cited previously) and **Eversmeyer** et al., (American Journal of Medicine. Aug. 1993, Vol. 95: 10S-18S; cited previously). The previous rejection over claims 38, 47, 48, 50-52, 62 and 63 is maintained for the reasons of record advanced in the previous office actions as well as for the reasons below. The rejection over claim 66 is necessitated by applicant's amendment to the claims. (Claim 66 recites limitations that are encompassed by the previously presented claim 51, and would have been rejected with the same references (as used for claim 51)).

Baker et al. teach pharmaceutical compositions for relieving pain in humans or mammals (e.g. mice, rats etc.) comprising a combination of:

a.) a narcotic analgesic (preferably oxycodone: see formulations col. 4-8; mice data in col. 8-10; patent claims), or a pharmaceutically acceptable salt thereof (reads on the salt of **clm 48**); and

b.) ibuprofen (a non-steroidal anti-inflammatory drug or NSAID: see col. 1-2), or a pharmaceutically acceptable suitable salt thereof,

in a weight ratio of about 1:800 (e.g. .001:1) to 1:1 (compare to present **claims 47** and **63**: See col. 2) with oxycodone amounts of about 5 mgs-600mgs (compare to present **claims 46** and **52**).

The Baker reference also teaches various dosage formulations such as the ones listed on column 4 (e.g. Examples 1-4), which tablet formulation "consists" of an oxycodone salt, Ibuprofen, and "at least one pharmaceutically acceptable excipient" including "microcrystalline cellulose", "starch", and "stearic acid". These formulations read on the oral dosage form of the instant **claim 38** except Ibuprofen is included instead of nabumetone. As recited in the various Examples (col.4), the amount of Ibuprofen (a NSAID compound) ranges from 60-300 mg, which range reads on the range recited in **claim 51**.

The dosage formulation of Baker also inherently teaches inclusion of oxycodone and at least one salt thereof as recited in **claim 62**, because it is an inherent property of the oxycodone salt (such as Oxycodone HCl) to comprise the Oxycodone compound itself. Thus, the formulation of the Baker reference comprises Oxycodone and at least a salt thereof.

The Baker reference further teaches oral administration (reads on the instant oral dosage form of **claim 38**), which can be co-administered in a single dosage form (e.g. see col. 3-8) or sequentially administered (e.g. see i.e. col. 8-9; mice are dosed sequentially...). The oral dosage forms include "sustained release" formulations (e.g. tablets, capsules, etc: see col. 3-4, especially col. 4), which reads on the sustained release

formulations of **claim 50**. The Baker et al. reference also teaches that dose ratios can be adjusted and that the analgesic activity of the combined oxycodone and ibuprofen activity is unexpectedly enhanced or synergistic i.e. the resulting activity is greater than the activity expected from the sum of the activities of the individual components, thereby permitting reduced dosages of narcotic analgesics (e.g. oxycodone) AND which diminishes adverse side effects (e.g. addiction) and toxicity which would result from the otherwise required amounts of the individual drug components resulting from high dosages of oxycodone or NSAID's such as ibuprofen. See e.g. col. 1-2; col. 3, lines 19-32). Accordingly, Baker would teach the use of therapeutic and sub-therapeutic amounts of oxycodone and/or ibuprofen in view of the synergistic nature of the combinations and the desire to reduce the toxicity and/or side-effects of both agents; and as required by the doctor for his/her particular patient., including dosage optimization e.g. dosage overlapping of active ingredients. See e.g. col. 3 where dosage is modified to suit the particular patient.

The Baker reference does not explicitly teach an oral analgesic composition comprising nabumetone instead of ibuprofen. The Baker reference also does not explicitly teach an oral dosage formulation comprising of nabumetone and at least one salt thereof as recited in the instant claims.

However, **Friedel** et al. teach that nabumetone (and/or pharmaceutical acceptable salt thereof) possesses the typical pharmacodynamic properties of the nonsteroidal class of anti-inflammatory (NSAID) drugs including intrinsic analgesic and antipyretic activity being demonstrated in animal studies and in humans with the following advantages over other NSAIDS:

a. does not exert a significant direct toxic effect on the gastric mucosa during absorption;

b. in studies, produced a lower incidence of gastrointestinal erosions or microbleeding than aspirin, naproxen, piroxicam and ibuprofen; and

c. more recently clinical data further confirmed the efficacy and tolerability of nabumetone ; "Thus, the drug (e.g. nabumetone and/or pharmaceutical acceptable salt thereof) should now be considered a well established member of this group of agents (e.g. NSAIDS) for the treatment of painful rheumatic and inflammatory conditions". See e.g. Abstract, pages 132-133 as well as the remainder of Friedel.

In addition, the Friedel reference also teaches various dosage amounts (such as 1000 mg-1500 mg) of nabumetone can be used for various treatment depending on the severity of the symptoms (e.g. p.133, bottom), which reads on the amount of nabumetone as recited in **claims 51** and **66**.

Similarly, **Eversmeyer** et al. teach that nabumetone is equally efficacious in the treatment of arthritic pain patients (e.g. osteo/rheumatoid arthritis) but has shown to be more safe, with reduced side-effects (e.g. dyspepsia, ulcers, reduced hemoglobin, gastritis etc.). See Eversmeyer et al. Abstract and disclosed studies.

Accordingly, one of ordinary skill in the art would have been motivated to substitute nabumetone and/or pharmaceutical acceptable salt thereof (a NSAID) for ibuprofen (a different NSAID) in the Baker reference compositions in light of the Friedel and/or Eversmeyer reference teachings that nabumetone is equally efficacious, but is safer with less side effects (e.g. as compared to ibuprofen).

Additionally, it is noted that the instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two (or more) compositions each of which is taught by the prior art to be useful for the same purpose.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the Baker reference analgesic composition by substituting the NSAID nabumetone with the appropriate amount (and/or pharmaceutical acceptable salt thereof) for the NSAID ibuprofen in light of the benefits of nabumetone (increased safety/decreased side effect as compared to ibuprofen) as taught by the Friedel and/or Eversmeyer reference references, to achieve the predictable result of formulating an analgesic oral dosage form for pain treatment. In addition, making and using compounds such as nabumetone and/or pharmaceutical acceptable salt thereof (as part of a combination drug) is routine and known in the art as taught by the cited references.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all cited references have demonstrate the success of making various pharmaceutical formulations comprising various analgesic compounds including oxycodone and nabumetone as well as various pharmaceutical acceptable excipients.

Discussion and Answer to Argument

10. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue "the cited references do not teach that nabumetone is safer than ibuprofen, and do not provide a reason for one skilled in the art to substitute ibuprofen..." (Reply, pp.7+).

Applicants are respectfully directed to the Supreme Court decision, which forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. *KSR, 127 S.Ct. at 1741, 82 USPQ2d at 1396.* ("Helpful insights, however, need not become rigid and mandatory formulas; and when it is so applied, the TSM test is incompatible with our precedents. The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents.")

As applicants have pointed out, the KSR decision requires "a reason" for combining the references (or elements). However, the KSR decision does not require that the "reasoning" be explicitly stated in the cited references. As long as it is "shown that those of ordinary skill in the art would have had some apparent reason to modify..." then a prima facie obvious case has been established.

Nevertheless, explicit motivation or reasoning statements are found in the cited references (see more discussion above and below). The previous office actions (especially, Office action, mailed 10/6/05; pp. 3+; and Office action mailed 8/1/06; pp.

10+) as well as the discussion supra have provided motivation statements and/or reasoning to combine the cited references. Contrary to applicant's assertion, "factual" supports are provided for the prima facie case of obviousness. Applicants are respectfully directed to the detailed discussion above on the specific teachings (or factual supports) of the cited references.

In addition, "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." (emphasis added; *KSR, 127 S.Ct. at 1741, 82 USPQ2d at 1396).*

Applicants also seem to argue the cited references "teaches away" form using nabumetone because of its "side effects". (Reply, pp.8+).

Applicants cited several passages in the Eversmeyer reference reciting occurrence of certain side effects.

First, applicants are not viewing the Eversmeyer reference as whole. Despite minor side effects, the Eversmeyer concludes that nabumetone is overall safer and have less impact in more serious side effects. The Eversmeyer reference states "In conclusion, nabumetone was demonstrated to be at least as safe as diclofenac… ibuprofen… as related to subjective complaints, such as dyspepsia or gastritis. However, more serious events, such as ulcers or meaningful descreases in hemoglovin, seem to occur less often

with nabumetone." (Eversmeyer, Abstract; emphasis added). In addition, Eversmeyer explicitly states "In conclusion, nabumetone was demonstrated to be as safe as diclofenac… ibuprofen… However, nabumetone maybe preferred in some patients because of the lower incidence of abdominal pain… and clinically meaningful diseases in hemoglobin." (Eversmeyer; p.17S; emphasis added). Thus, the overall teaching of the Eversmeyer reference does not constitute as "teaching away", and the reference clearly provides explicit motivation or reasoning to substitute nabumetone for ibuprofen due to its overall safety and reduction in side effects.

Applicants also cited several passages from the Friedel reference to demonstrate nabumetone is not safer than ibuprofen (Reply, ppp.10+).

Similar to the discussion above for the Eversmeyer reference, applicants did not view the Friedel reference as a whole. The Friedel reference states "Overall, nabumetone administration is associated with a relatively low incidence of gastric ulceration, and an incidence of perforation which may be lower than that seen with some other NSAIDs" and "Thus, continued clinical experience has provided further support for the favourable profile of efficacy and tolerability apparently initially, and has confirmed the place of nabumetone…" (Freidel, p.153; emphasis added).

Contrary to applicant's assertion, the Friedel reference, similar to the Eversmeyer reference, provides explicit motivation statement (i.e. stating the advantages of nabumetone) to use nabumetone from the class of NSAIDs compounds.

Applicants also seem to argue the KSR reasoning of "obvious to try" is not applicable in the instant case, because there is not a "finite number of identified, predictable solutions." (Reply, p.9+).

First, the "obvious to try" rationale is only one of the many reasoning statements to combine the references presented previously (as well as above).

Further, applicants questioned the potential number of "solutions" based on the Baker reference alone. However, the above rejection is based on a combination of references. For example, the Eversmeyer reference discloses a "finite" number of five NSAIDs that were compared. It would have been obvious to try a combination of oxycodone and each one of the four NSAIDs to achieve the predictable result of providing synergistic effects.

Applicants also argue nabumentone is not an equivalent of ibuprofen based on the Baker's teachings. (Reply, p.9).

However, the above rejection is not just based on the Baker reference alone. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants argue the modification/combination would render the Baker reference unsatisfactory for its intended purpose". (Reply, pp.11+).

Contrary to applicant's assertion, the combination of the reference would not destroy the purpose of the Baker reference for making and using pharmaceutical compositions constituting a combination of a narcotic analgesics (such as oxycodone) and a NSAID (such as ibuprofen). The purpose of the reference is in general to make and use pharmaceutical compositions with various combinations of narcotic analgesics and NSAID so that synergistic and/or additive effects of the combinations of the drugs can be utilized. For example, the Baker reference states "This patent discloses that the analgesic effect of the combination of a selected NSAID and a selected narcotic analgesic is greater than for either alone..." (Baker, col.1, lines 22+). The Baker's teaching of using a particular combination of Oxycodone and Ibuprofen is only one embodiment of the reference's teaching, and it is not the sole purpose of the reference's teaching. By substituting one NSAID compound such as Ibuprofen with another NSAID drug such as Nabumetone to produce a pharmaceutical composition that has "greater" analgesic effects than for either alone (as stated by Baker) does not defeat the general purpose of making and using a pharmaceutical composition comprising two selected active ingredients (to achieve synergist/additive effects).

Applicant's interpretation of the Baker patent reference fails to consider the Baker patent teaching as a whole to one of ordinary skill in the art:

> "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." In re Heck, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting In re Lemelson, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)). A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). See also Celeritas

Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998).

Accordingly, the Baker teaching includes Baker's entire specification and claims, inclusive of Baker's summary of the state of the prior art as illustrated in the "The Background of the Invention" (col. 1-2). In this respect, Baker '936 (col. 1-2) cites numerous prior art references starting with Sunshine et al. for the premise of making analgesic compositions by combining NSAID"s with narcotic analgesic (distinguished by merely additive analgesic effect) as well as other NSAID's (e.g. acetaminophen etc) with various narcotic analgesics, most notably oxycodone. Baker's invention (e.g. following the summary) is distinguished from the prior art by selecting compositions comprising ibuprofen as the NSAID in combination with narcotic analgesics (including oxycodone) in synergistically effective amounts while reducing the amounts of the narcotic analgesic thus addressing the problem of addiction (pointed to at the end of the "Background of the Invention").

As stated in MPEP 2143.01 and provided by the case law:

"The court reversed the rejection holding the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." 270 F.2d at 813, 123 USPQ at 352.)." (emphasis added)

In this case, the combination of the cited references would not require "a substantial reconstruction and redesign of the elements" in the primary reference (i.e. the Baker reference). Applicant's argument regarding the exclusion of ibuprofen is irrelevant

because the combination of the cited references "substitutes" ibuprofen for nabumetone to achieve the predictable synergistic effects, as taught or evidenced by the cited references discussed supra. The principle of operation in Baker is making and using a pharmaceutical composition having one narcotic analgesic (such as Oxycodone) and one NSAID compound (such as ibuprofen or nabumetone) to achieve a synergistic effect. The Friedel and Eversmeyer references provide further reasoning or motivation (e.g. the advantages of using Nabumetone) to make the modification or substitution of the Baker pharmaceutical composition as discussed above. Thus, the combination of the cited references does not change the principle of operation in Baker.

Applicants also argue because nabumetone is not mentioned anywhere in Baker, the above rejection is improper. (Reply, pp.12+).

However, the above rejection is not just based on the Baker reference alone. The missing element of nabumetone is supplied with the other cited references.

The purpose of the Baker reference is to combine NSAID's (e.g. ibuprofen) with opioids (e.g. oxycodone) in order to achieve improved pain relief as compared to the separate administration of the active agents. The unexpected benefit of achieving greater than additive pain relief (e.g. synergism) represents a strong teaching toward formulating additional compositions which include different (functionally equivalent) NSAID's, especially those with fewer side-effects as compared to traditional NSAID's as pointed out in the secondary reference (Eversmeyer et al; e.g. Abstract of the reference).

In addition,

> Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). See also MPEP 2121.04.

As discussed above, Baker et al teaches combinations of narcotic analgesics and NSAIDs (see col. 1-2), and do not exclude other NSAIDs from forming the combination of narcotic analgesic and NSAID that would have enhanced analgesic effect. In other words, the Baker reference does not teach that a combination of a narcotic analgesic and any of the other NSAIDs (besides ibuprofen) cannot be made or cannot be used to treat pain.

Rather, the Baker reference opens the door for developing combinations of NSAIDs and narcotic analgesics beside the combinations of ibuprofen and oxycodone. As discussed above, Baker teaches, in general, a combination of a selected NSAID and a narcotic analgesic would have enhanced analgesic effect (col. 1, lines 22+). Baker et al also demonstrated a particular combination of the two classes of drug has enhanced analgesic effect. A person of ordinary skill in the art would be motivated to select different NSAID and/or a different narcotic analgesic to form a desired combination with enhanced analgesic effect.

Applicants also requested an explicit citation for "synergistic effect between nabumetone and oxycodone" from the cited references. However, as discussed above, explicit motivation/reasoning statement need not come from the cited references (see KSR). As discussed above, Baker teaches, in general, a combination of a selected NSAID and a narcotic analgesic would have enhanced analgesic effect (col. 1, lines 22+). And the Friedel and Eversmeyer references teach nabumetone is a "preferred" NSAIDs

or nabumetone offers advantages such as less major side effects (e.g. Eversmeyer; Abstract). Thus, one of ordinary skill in the art would have been motivated or have a reason to combine the cited references to form a pharmaceutical composition of nabumetone and oxycodone for the synergistic effect.

See MPEP 2143:

"The claimed invention in In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982) was directed to a method for decaffeinating coffee or tea. The prior art (Pagliaro) method produced a decaffeinated vegetable material and trapped the caffeine in a fatty material (such as oil). The caffeine was then removed from the fatty material by an aqueous extraction process. Applicant (Fout) substituted an evaporative distillation step for the aqueous extraction step. The prior art (Waterman) suspended coffee in oil and then directly distilled the caffeine through the oil. The court found that "[b]ecause both Pagliaro and Waterman teach a method for separating caffeine from oil, it would have been prima facie obvious to substitute one method for the other. Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious." Id. at 301, 213 USPQ at 536." (emphasis added).

Applicants also argue "these amounts [1000mg-1500mg] exceed the per unit amount of active ingredient taught by the Baker reference". (Reply, p.12+).

Again, applicants traversed the rejection by arguing one of the cited references. The range of the amount of the active ingredient cited by applicants is only one embodiment of the Baker's reference's teachings. In addition, the Friedel and Eversmeyer reference teaches amounts such as 1000mg. As discussed above, the Friedel reference also teaches various dosage amounts (such as 1000 mg-1500 mg) of nabumetone can be used for various treatment depending on the severity of the symptoms (e.g. p.133, bottom). Further, Eversmeyer states "it is evident that the dose of nabumetone can be increased as needed to control symptoms without a concordant increase in the incidence of adverse events." (Eversmeyer, p.17S, bottom). Thus, it would have been

obvious for one of ordinary skill in the art to generate a dosage form with the appropriate amount of nabumetone to achieve the predictable result of treating the various symptoms without increased incidence of "adverse events".

Baker and others con't

11. Claims **38** and **47-67** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Baker** et al., (US Patent 4,569,937; 2/11/1986; cited previously), **Friedel** et al (Drugs. 1993. Vol. 45 (1): 131-156; cited previously) and **Eversmeyer** et al., (American Journal of Medicine. Aug. 1993, Vol. 95: 10S-18S; cited previously) as applied to claims 38, 47, 48 and 50-52 above, and further in view of **Oshlack** et al. US Pat. No. 5,472,712 (12/95) or **Oshlack** et al. US Pat. No. 6,294,195 (9/01: effectively filed 10/93 or earlier). The previous rejection over claims 38 and 47-65 is maintained for the reasons of record advanced in the previous office actions as well as for the reasons below. The rejection over claims 66 and 67 is necessitated by applicant's amendment to the claims. (Claims 66 and 67 recite limitations that are encompassed by the previously presented claim 51, and would have been rejected with the same references (as used for claim 51)).

The substance of the above obviousness rejection (the rejection over the combination of Baker, Friedel and Eversmeyer) is hereby incorporated by reference in its entirety.

Although the Baker reference teaches oral dosage forms which include "sustained release" formulations (e.g. tablets, capsules, etc: see col. 3-4, especially col. 4) utilizing

"sustained release carriers", the Baker reference does not explicitly teach "a sustained release carrier which provides a sustained release of the oxycodone and/or ... salt thereof" and "a sustained release of the nabumetone..." as recited in the instant claims 49, 59, 64, 65 etc. The Baker reference also does not explicitly teach using "an immediate release form" for nabumetone in the formulation (as recited in the instant claim 53) as well as formulation comprising particles of 0.5 to 2.5 mm in diameters as recited in the instant claims 57 and 58.

However, the use of sustained release dosage forms for opioid analgesics, including oxycodone such as utilizing sustained release carriers, beads (or particles with various diameters) as well as using immediate release formulation for non-opioid drugs in a combination drug formulation are known and routine in the art. Using beads/particles coated with the opioid drug including substrate layers which comprise the drugs is also known in the art to produce delayed release of extended duration. For examples, **Oslack** et al ('712 patent) teach drug formulation of sustained (or controlled) release formulation of various compounds including the controlled release of oxycodone (e.g. col.14, lines 15+); Oslack et al ('195 patent) also teach sustained oral formulation for opioid analgesics (e.g. Abstract) including oxycodone (e.g. col.6, lines 30+). The Oslack ('195) patent specifically teach using particles with diameters of about 0.1mm to about 3 mm (e.g. Abstract), which reads on the particles of **clms 57** and **58**. The Oslack ('195) patent also teaches using "immediate release" formulation for "a second (non-opioid) drug", incorporated into immediate release layer, or coating, etc. (e.g. col.7, lines 21+), which reads on the immediate release formulation of **clm 53** and the coating layer of **clm 59**. The Oslack ('195) reference also teaches incorporating sustained release matrix with the

opioid drug (e.g. col.11, lines 30+), which reads on the sustained carrier of **clm 60**. The Oslack ('195) reference also teaches various sustained release carrier such as "hydroxyalkylcellulose" (e.g. col.11, lines 34+), which reads on the sustained carrier of **clm 55**. The Oslack ('195) reference also teaches the sustained release formulations provide about at least 12 hour or about 24 hours, or longer release time for opioid drugs (e.g. col.5, lines 40+), which reads on the release time of **clms 54** and **61**. The Oslack ('195) reference also teaches treating pain for cancer patients (e.g. col.1, lines 50+), which the cancer pain reads on the types of pains listed in **clm 56**. Both of the references also teach the advantages of sustained release formulation. For example, the '195 patent teaches the controlled or sustained release oral dosage formulation would provide effective blood levels of the opioid analgesic for at least about 24 hours (e.g. Abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to utilize various known and routine formulations to make various analgesic compositions that have various release rates. For examples, the sustained release carriers for oxycodone including beads/layers as well as the immediate release formulations for the other non-opioid drug in the same formulation as taught by the Oshlack and Oshlack et al. patents. A person of ordinary skill in the art would have been motivated at the time of the invention to use the various formulations as disclosed in Oshlack references (i.e. the various time releasing formulations) to make a combination drug based on a sustained releasing opioid drug (such as oxycodone) and an immediate releasing non-opioid drug (such as nabumetone), because Baker et al and Oshlack ('195) patent specifically teach "sustained release formulations" for the opioid drug is known and routine, and the advantages of utilizing the Oshlack patent sustained release carriers

including delayed drug release of extended duration especially for treatment of cancer pains. In addition, it would have been obvious to one of ordinary skill in the art to apply the standard technique of formulating sustained release formulation (especially for oral administering an opioid analgesic such as oxycodone) as taught by both the Oshlack patent references, to improve the delivery of the analgesic compounds for the predicable result of enabling standard pharmaceutical formulation and administering.

A person of ordinary skill in the art would have been motivated at the time of the invention to use immediate or sustained release formulation for the non-opioid drug (such as Nabumetone) in the same combination drug formulation, because Oshlack ('195) patent teaches the advantages of using immediate release formulation such as an "immediate releasing layer" to coat the opioid drug to afford differential drug release rates for efficient pain treatments. In addition, because all the cited references teach methods of making various combinations of drugs in the same pharmaceutical composition with various releasing matrices, coating, particles, etc., for various pain treatments, it would have been obvious to one skilled in the art to substitute one type of releasing formulation (such as sustained release) for the other (such as immediate release or combinations of sustained and immediate release formulations) to achieve the predictable result of making pharmaceutical composition with optimized drug releasing rates.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all of the cited references have demonstrated the success of making and using various drug formulations (including sustained/immediate

release formulations, coating, tablets, particle matrix, etc.) especially for various analgesic compounds.

Discussion and Answer to Argument (103 art rejection)

12. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants traversed the above rejection with the same argument as the traversal over the combinations of "Baker, Friedel and Eversmeyer" references. Thus, applicants are respectfully directed to the discussion under "Baker, Friedel and Eversmeyer" for answer to arguments.

Applicants also assert the combination of the cited references does not each the limitation of claim 59. However, applicants have not provided reason for this assertion. Applicants are directed to the above rejection for discussion how the combination of the cited references render the instant claimed invention (including limitation in claim 59) obvious.

Mayer and Others

13. Claims **38, 47-52** and **62-66** are rejected under **35 U.S.C. 103(a)** as being unpatentable over **Mayer** et al (US 5,840,731; 11/24/1998; filed on 8/2/1995; cited previously), and if necessary in view of **Friedel** et al (Drugs. 1993. Vol. 45 (1): 131-156; cited previously) and **Eversmeyer** et al., (American Journal of Medicine. Aug. 1993,

Vol. 95: 10S-18S; cited previously). The previous rejection over claims 38, 47-52 and 62-65 is maintained for the reasons of record advanced in the previous office actions as well as for the reasons below. The rejection over claim 66 is necessitated by applicant's amendment to the claims. (Claim 66 recites limitations that are encompassed by the previously presented claim 51, and would have been rejected with the same references (as used for claim 51)).

Mayer et al, throughout the patent, teach methods of treating pain using various drug compositions (see Abstract; Claim 2), which reads on the claimed treatment method of **clms 38** and **62**.

The reference also teaches the compositions of drugs can be combinations of drugs (e.g. col.1, lines 24+), and especially combination between Opioid analgesics and NSAIDS (e.g. col.1, lines 50+). The reference also teaches "the first component of the drug composition" is an opioid such as "oxycodone" and/or their pharmaceutically acceptable salts (e.g. col.3, lines 57+). The reference also teaches "the second component of the drug composition" is "of the nonopioid type… of any of the foregoing" (col.4, lines 11+), and the reference discloses the nonopioid analgesics includes "nabumetone" and/or its pharmaceutically acceptable salts (col.3-4; bridging). These passages of the reference teach a composition for pain treatment comprising oxycodone and nabumetone of **clms 38** and **62.**

The reference also teaches pharmaceutical acceptable carriers (e.g. col. 5), which reads on the component of **clms 38**, **48** and **62**. The reference also teaches, for example, 4.5 mg of oxycodone (see Table in between cols. 5-6), which reads on the dosage amount of **clm 52**.

The reference also teaches various amounts of the "first" and "second" components of the drug (e.g. col.5-6; Examples), which read on the ratios recited in **clms 47** and **63**.

The reference also teaches using various drug formulations such as gelatin capsules (e.g. col.5, lines 5+), which reads on the sustained release carriers of **clms 49, 50, 64** and **65**.

The Mayer reference does not explicitly teach using "an oral dosage form consisting of (i) nabumetone… (ii) oxycodone… and (iii) at least one pharmaceutically acceptable excipient" as recited in **clms 38** and **62**.

However, the Mayer reference teaches a number of drug combinations for alleviating pain… are known" (e.g. col.1, lines 24+). As discussed supra, the Mayer reference also teaches combination of an opioid drug such as oxycodone and a NSAID drug such as nabumetone is known in the prior art to be effective analgesic (e.g. cols.3-4). In addition, the Mayer reference also teaches the necessary ingredient of pharmaceutically acceptable excipient as part of a pharmaceutical composition (e.g. col.5).

In addition, **Friedel** et al. teach that nabumetone (and/or pharmaceutical acceptable salt thereof) possesses the typical pharmacodynamic properties of the nonsteroidal class of anti-inflammatory (NSAID) drugs including intrinsic analgesic and antipyretic activity being demonstrated in animal studies and in humans with the following advantages over other NSAIDS:

a. does not exert a significant direct toxic effect on the gastric mucosa during absorption;

b. in studies, produced a lower incidence of gastrointestinal erosions or microbleeding than aspirin, naproxen, piroxicam and ibuprofen; and

c. more recently clinical data further confirmed the efficacy and tolerability of nabumetone ; "Thus, the drug (e.g. nabumetone and/or pharmaceutical acceptable salt thereof) should now be considered a well established member of this group of agents (e.g. NSAIDS) for the treatment of painful rheumatic and inflammatory conditions". See e.g. Abstract, pages 132-133 as well as the remainder of Friedel.

In addition, the Friedel reference also teaches various dosage amounts (such as 1000 mg-1500 mg) of nabumetone can be used for various treatment depending on the severity of the symptoms (e.g. p.133, bottom), which reads on the amount of nabumetone as recited in **claim 51**.

Similarly, **Eversmeyer** et al. teach that nabumetone is equally efficacious in the treatment of arthritic pain patients (e.g. osteo/rheumatoid arthritis) but has shown to be more safe, with reduced side-effects (e.g. dyspepsia, ulcers, reduced hemoglobin, gastritis etc.). See Eversmeyer et al. Abstract and disclosed studies.

Accordingly, one of ordinary skill in the art would have been motivated to combine nabumetone (a NSAID) and/or pharmaceutical acceptable salt thereof with Oxycodone (an opioid analgesic) in light of the Mayer, the Friedel and/or Eversmeyer reference teachings that nabumetone is equally efficacious, but is safer with less side effects.

Additionally, it is noted that the instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court

held that it is *prima facie* obvious to combine two (or more) compositions each of which is taught by the prior art to be useful for the same purpose.

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to make and use an oral dosage form consisting of only oxycodone and nabumetone with at least one pharmaceutically acceptable excipient.

A person of ordinary skill in the art would have been motivated at the time of the invention to make and use an oral dosage form consisting of only oxycodone and nabumetone (with an appropriate amount) with at least one pharmaceutically acceptable excipient, because dosage forms of combinations of analgesic drugs (such as oxycodone and nabumetone) are routine and known in the art. In addition, the Mayer reference teaches the advantages of making and using pharmaceutical composition comprising a combination of an opioid drug and a NSAID drug so that a synergistic effect can be achieved. Further, the Friedel and/or Eversmeyer references teach the advantages of Nabumetone. Because the Mayer reference teach methods of making and using various drug formulation comprising different combinations of an opioid drug and a NSAID drug, it would have been obvious to one skilled in the art to substitute one drug for the other to achieve the predictable result of making and using routine analgesic pharmaceutical composition. It would have been obvious to one of ordinary skill in the art to apply the standard technique of adding at least one "pharmaceutically acceptable excipients" as taught by Mayer et al, to improve pharmaceutical formulation for the predicable result of enabling standard making and using a pharmaceutical composition for treatment of pain.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since Mayer et al have demonstrated the success of generating and using various pharmaceutical formulations.

Discussion and Answer to Argument (103 art rejection)

14. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue the cited combination of references does not teach the instant claimed because the "consisting of" language excludes the receptor antagonist that is included in the Mayer reference. (Reply, pp.14+).

However, the above rejection is not an anticipatory (i.e. under 35 USC 102(e)) over the Mayer reference alone. The above rejection is an obviousness rejection over a combination of cited references. Applicants are respectfully directed to the above rejection for discussion on how the combination of the cited references renders the instant claimed invention obvious.

Conclusion

15. This is a continuation of applicant's earlier Application No. 10/056,348. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL**

even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Sue Liu/
Primary Examiner, AU 1639
6/17/09